Acute Kidney Injury Post kidney Transplantation

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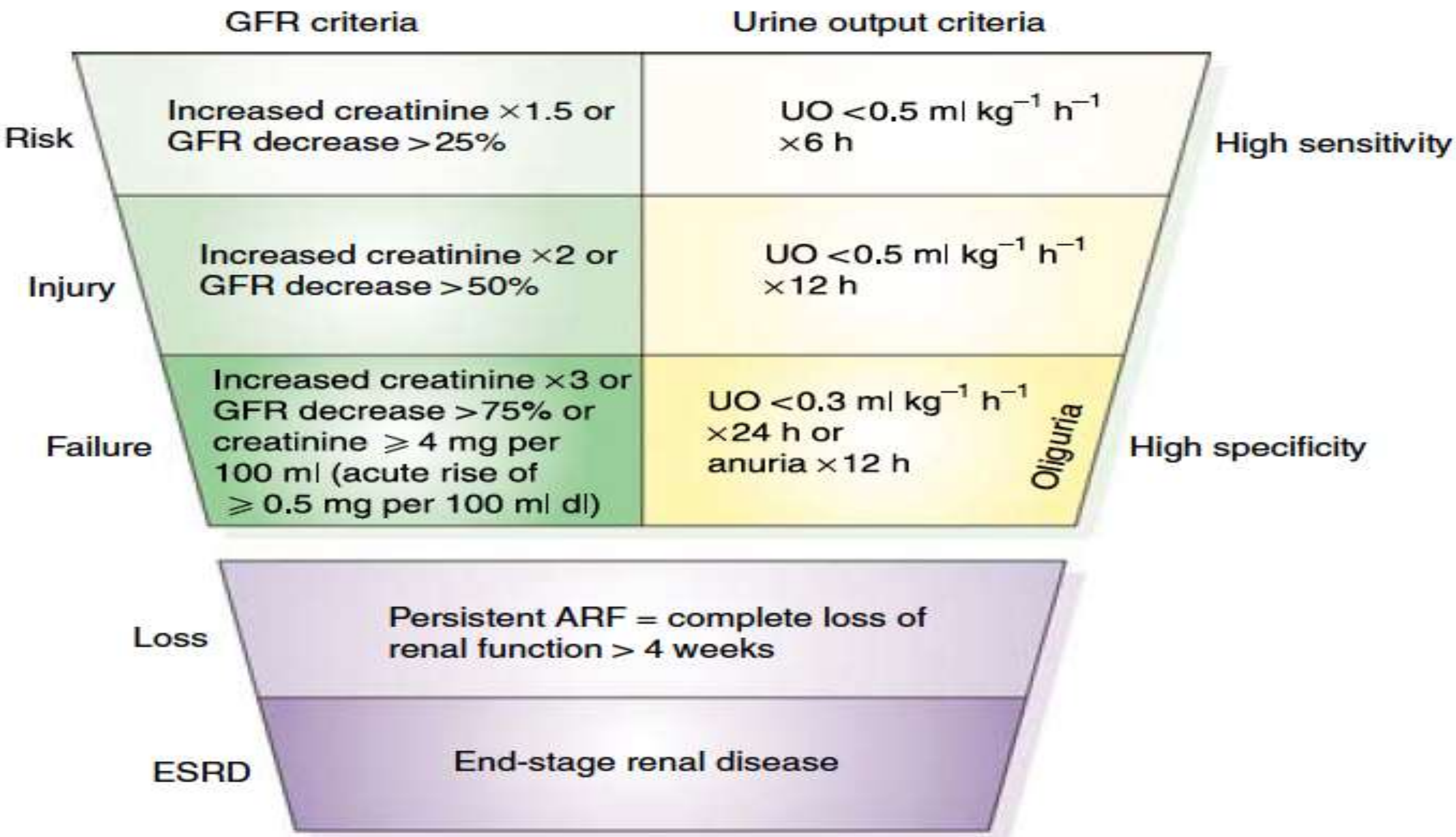
Agenda

- Definitions
- Relevance
- Causes
- Pathophysiology
- Diagnosis
- Management and Updates

Definitions

- Abrupt loss of kidney function that results in the retention of urea and other nitrogenous waste products and in the dysregulation of extracellular volume and electrolytes
- DGF is purest form

Definitions



Relevance

- Incidence up to 20%
- Same as native + rejection and IRI
- Major risk factor for graft loss
- Severity of AKI (RIFLE) was correlated to the graft outcome
- Increased mortality

Nakamura M, et al. Clin Transplant 2012
Mehrotra A. Am J Kidney Dis. 2012

Relevance

Clin Transplant 2012: 26: 520–528 DOI: 10.1111/j.1399-0012.2011.01546.x

Clinical Transplantation

Acute kidney injury as defined by the RIFLE criteria is a risk factor for kidney transplant graft failure

Nakamura M, Seki G, Iwadoh K, Nakajima I, Fuchinoue S, Fujita T, Teraoka S. Acute kidney injury as defined by the RIFLE criteria is a risk factor for kidney transplant graft failure.

Abstract: Acute kidney injury (AKI) is not recognized as a major complication at the maintenance phase after kidney transplantation (KTx). Moreover, it is not clear whether the onset of AKI leads to graft failure. We examined the incidence of AKI that developed three months or later after KTx at our institute. We examined whether the incidence of AKI defined by the Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease criteria associates with graft failure by matched-pair Cox regression analysis. A total of 289 patients were available for the final analysis. The overall incidence of AKI was 20.4%, and the common etiology of AKI was bacterial infectious diseases. The group that developed AKI had significantly lower

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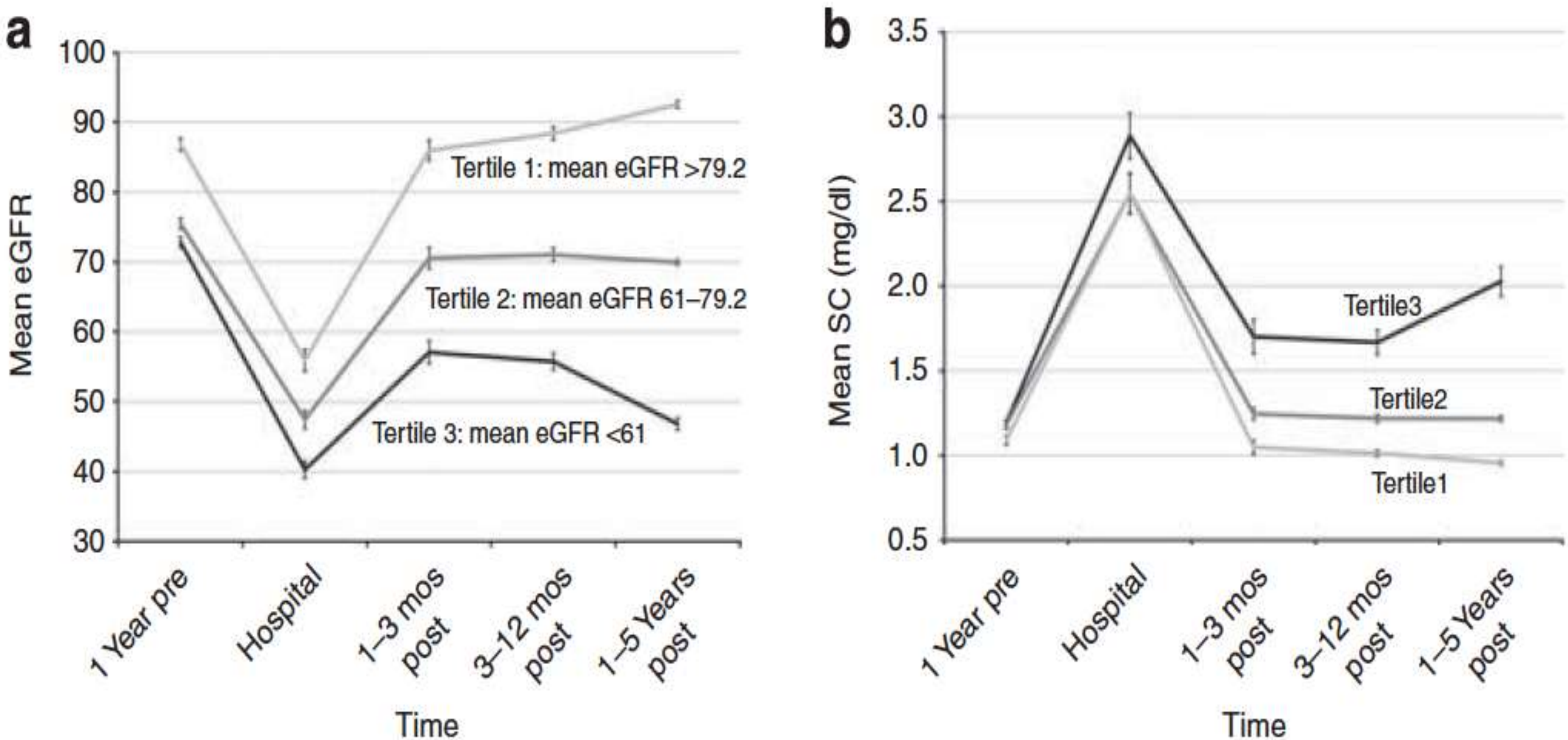
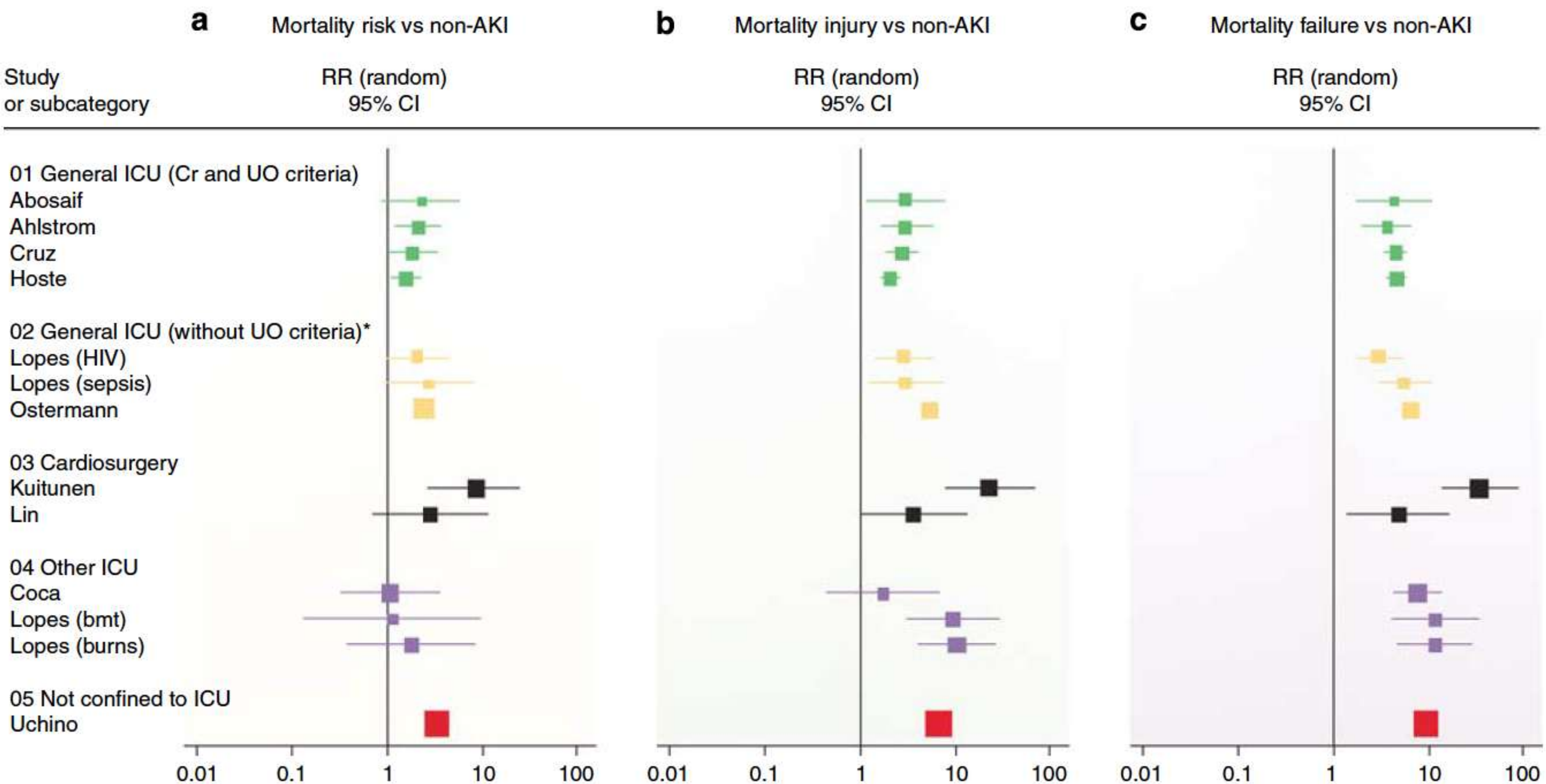
Key words: acute kidney failure – graft survival – infection – kidney transplantation – rejection

Relevance

http://www.kidney-international.org original article



Relevance



Ricci Z. et al, Kidney international; 2008

Causes

- Pre-renal
  - Volume depletion, hypotension
  - Calcineurin inhibitor effects
- Renal
  - Delayed graft function
  - Acute rejection
  - Cellular and Antibody-mediated
  - Recurrent primary kidney disease
  - Infection (UTI) Polyoma virus (BK)
- Post-renal
  - Obstruction

Causes

- **Immediate**: First week
  - Antibody-mediated rejection.
  - Acute cellular rejection.
  - Acute tubular necrosis.
  - Drug toxicity.
  - DGF

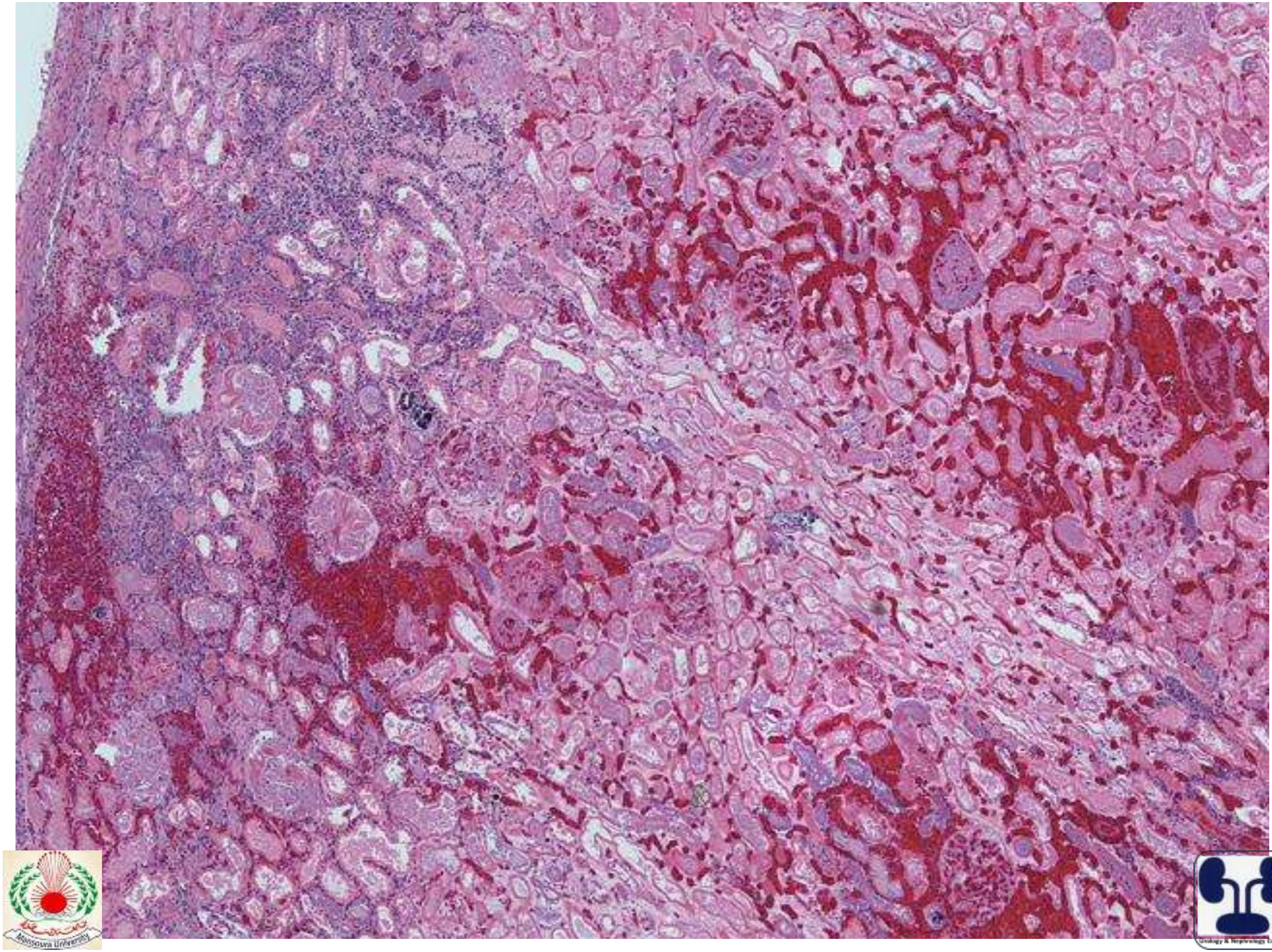
Acute Humoral Rejection

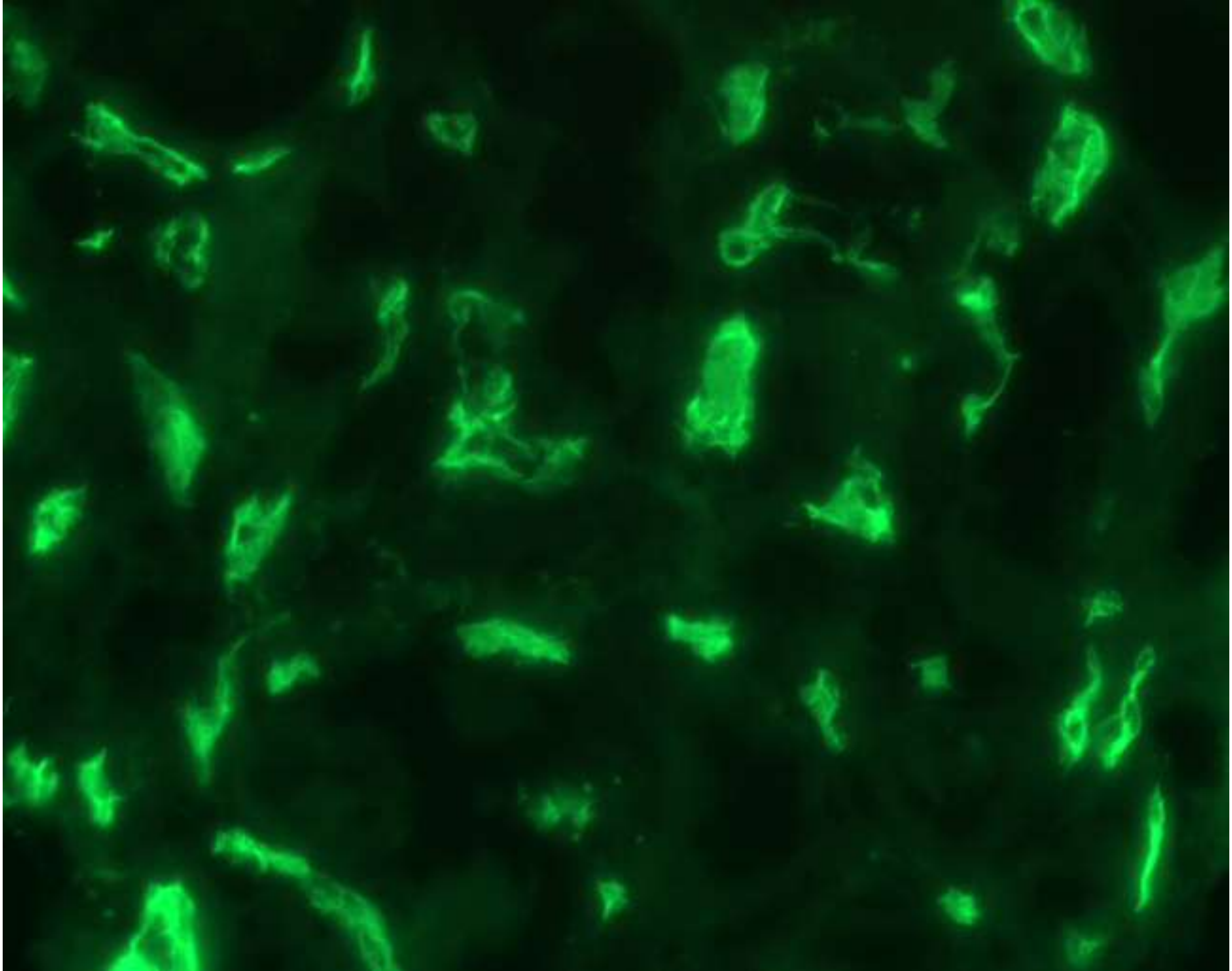
Timing → non functioning graft, early or later

Associated with significant graft loss

Increased frequency

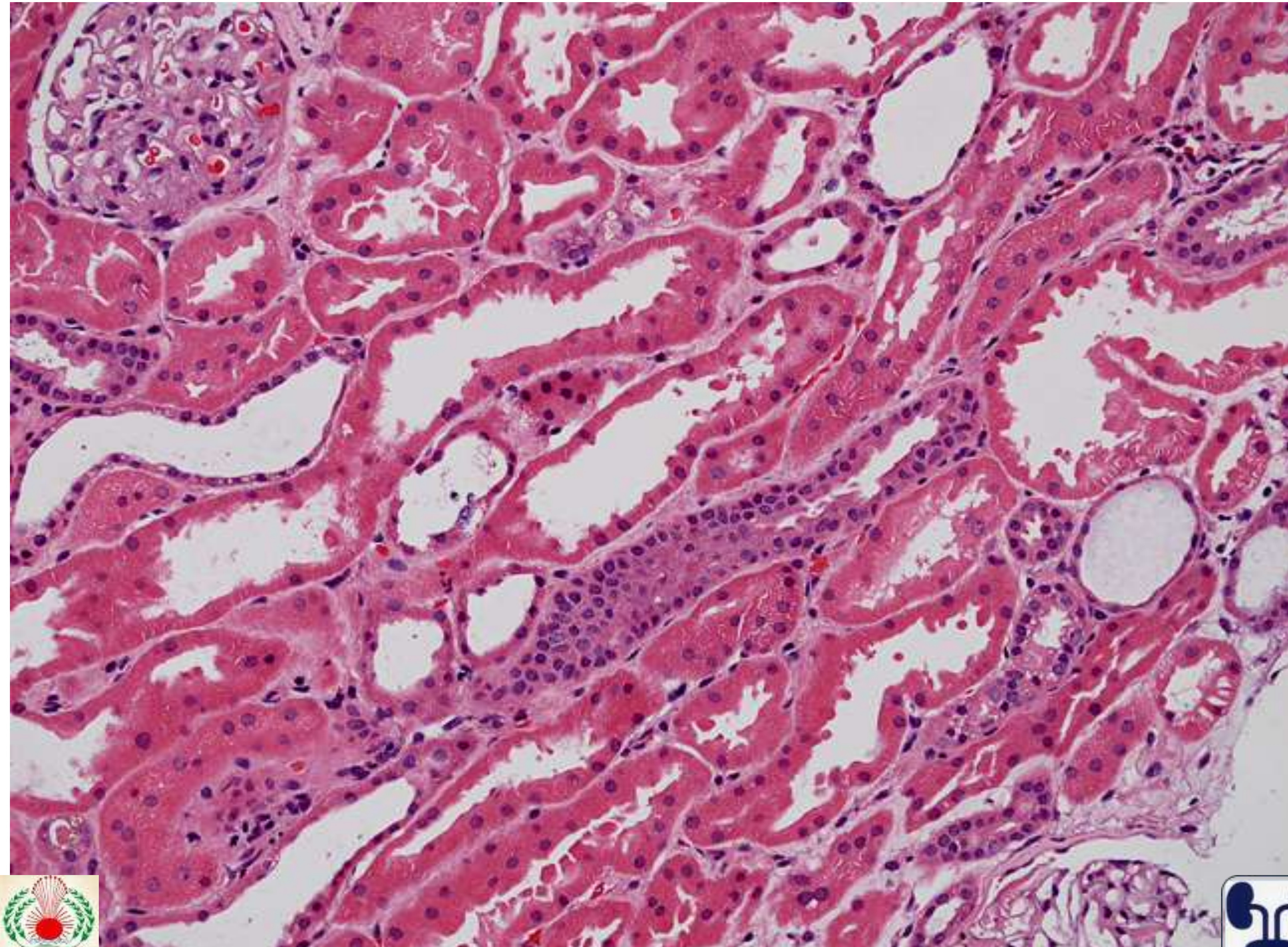
- Recognition of entity
- Better techniques for detection
- More retransplanted patients
- Transplantation across barriers





Acute Tubular Necrosis

- Graft injury due to lack of perfusion.
- Increased with longer cold ischemia time.
- May be seen in association with vascular anastomosis problems or obstruction (e.g. lymphocele).



EARLY

- 6 months :
  - Acute rejection.
  - Drug toxicity.
  - Infection.

Acute Cellular Rejection

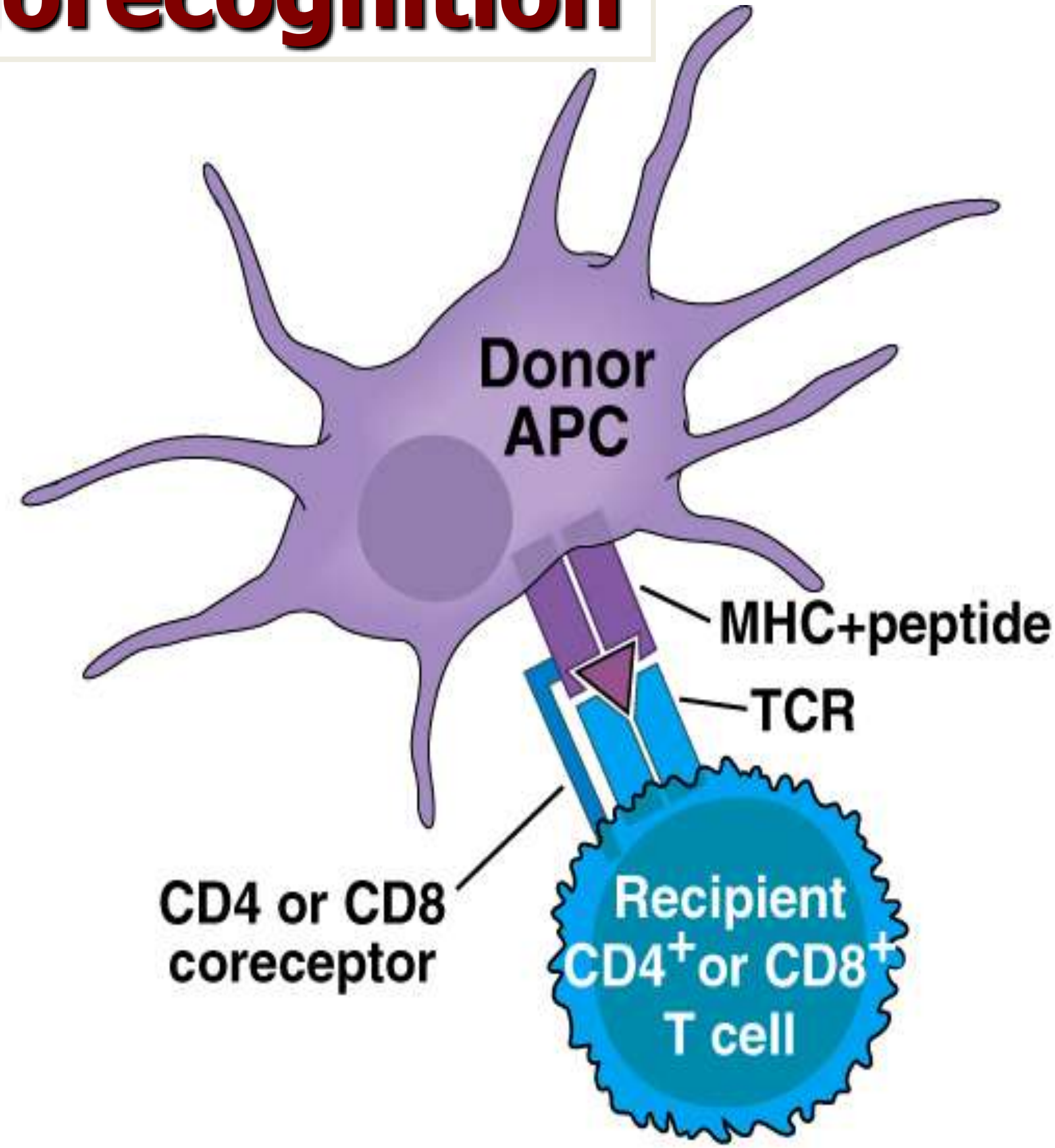
Pathogenesis

- Cell-mediated.
  - Chiefly T-cells
- May co-exist with humoral rejection.

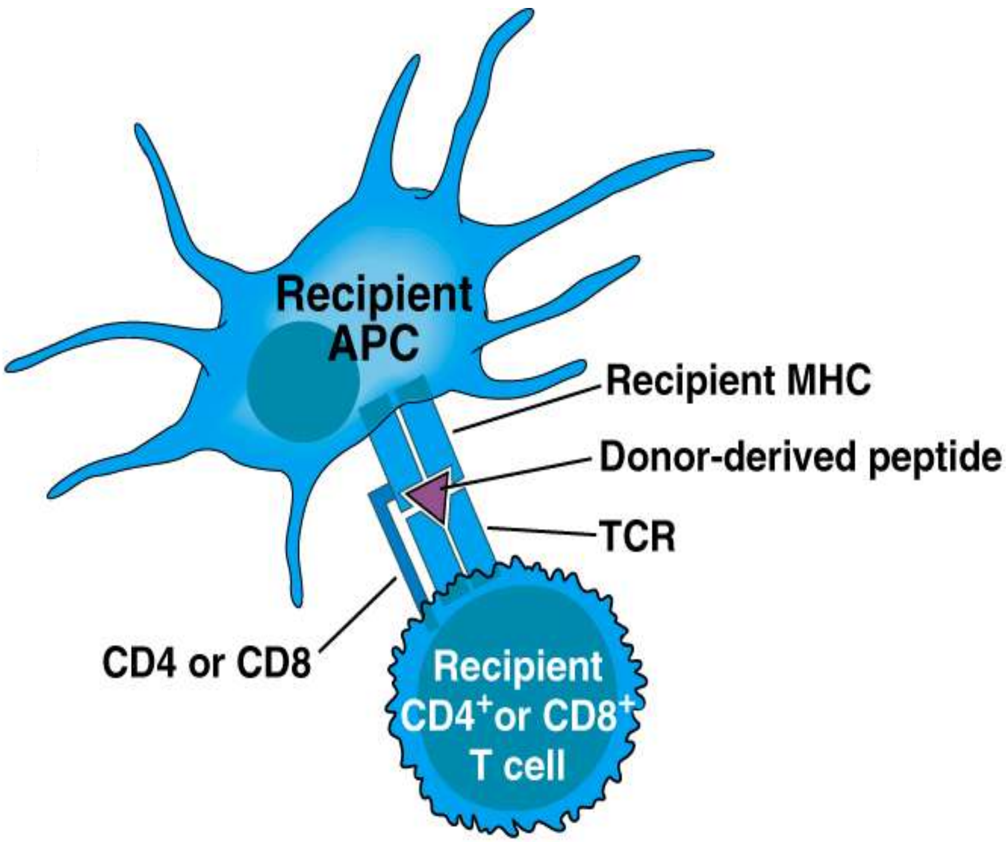
Clinical

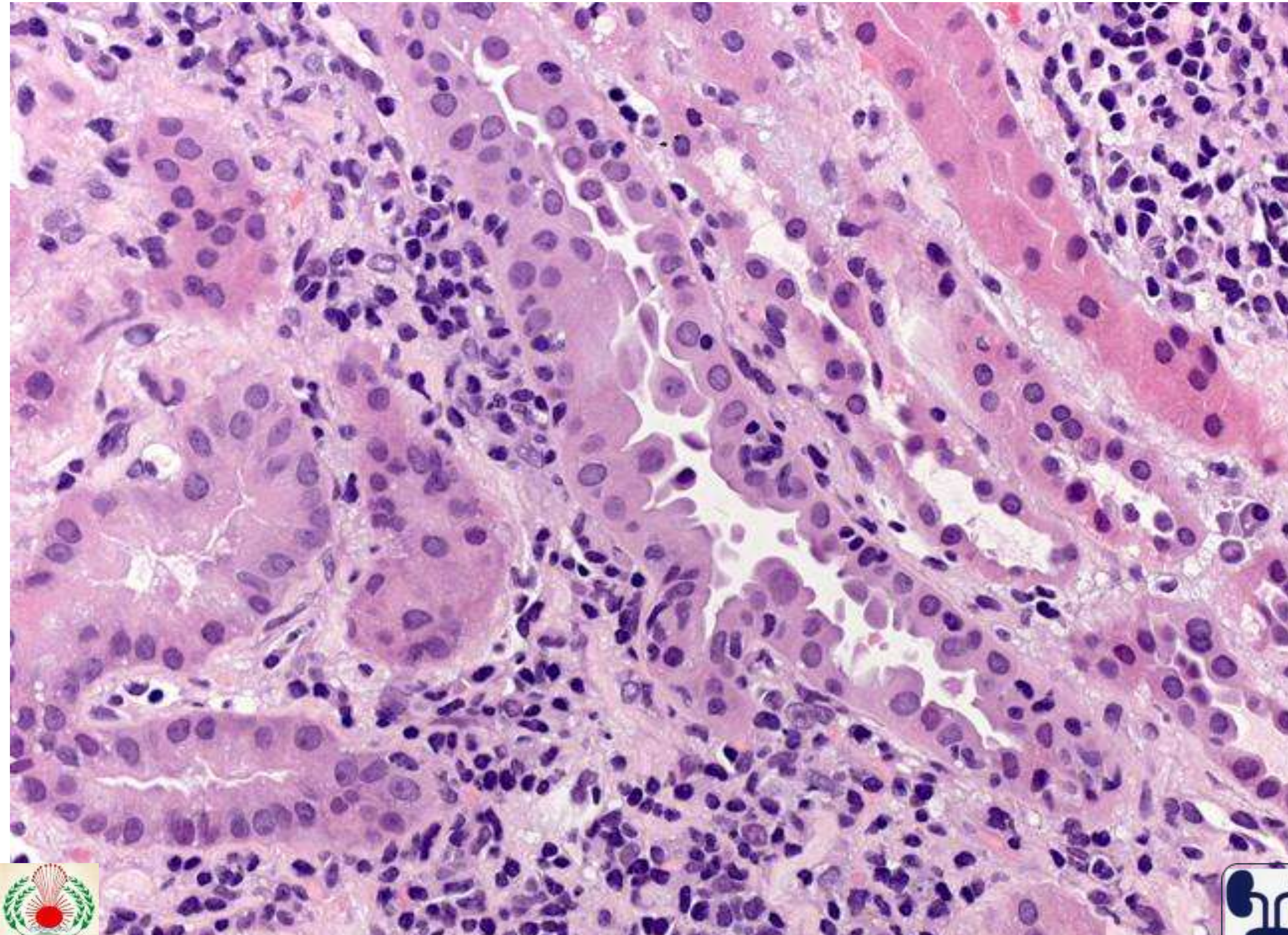
- Rise in serum creatinine.
- Graft tenderness.

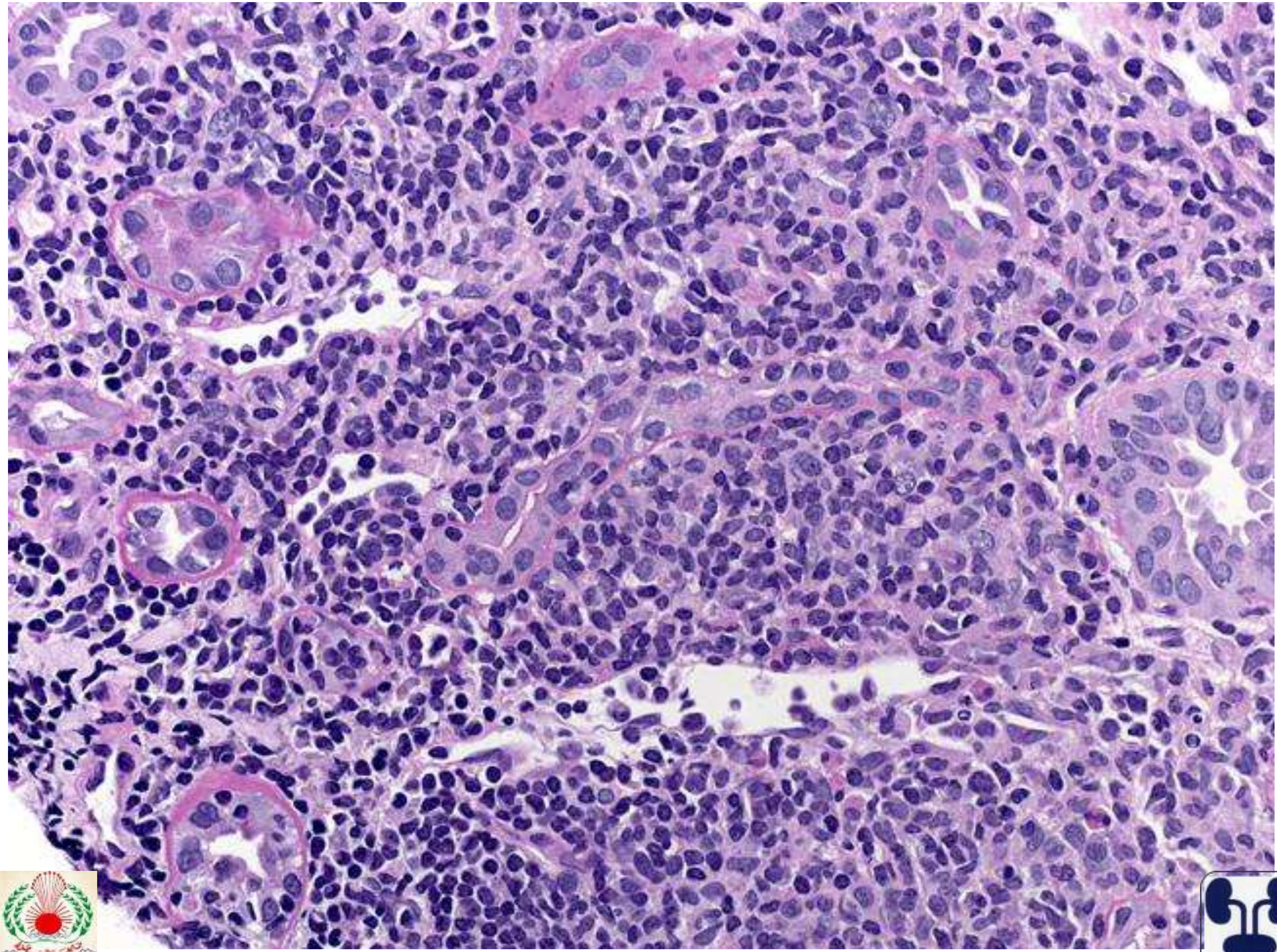
Direct Allorecognition



Indirect Allorecognition







Drug Toxicity

Calcineurin inhibitors.

Acute.

Thrombotic microangiopathy –

Peripheral hyalinization.

Chronic.

Striped fibrosis.

Intimal thickening.

Double contours in glomeruli.

Drug Toxicity

- OKT3
  - Fibrin thrombi.
- Rapamycin
  - Cast nephropathy.
- IVIG
  - Tall vacuolated epithelial cells.
- Antibiotics
  - Acute interstitial nephritis.

Infection

Pyelonephritis

- Neutrophils in tubules and interstitium.

Viruses

- May affect ureter and cause necrosis.
- Polyoma, CMV, adenovirus.

Fungi

Polyoma V. (BK)

90% worldwide

Persists in urinary tract-20-60% of immunocompromised

Polyoma nephropathy in 1-10% renal tx

Risk factors

- Intensity of immunosuppression
- Recipient-male, age>50, seronegative
- Graft-seropositive, HLA mismatch, ischemic or immune injury

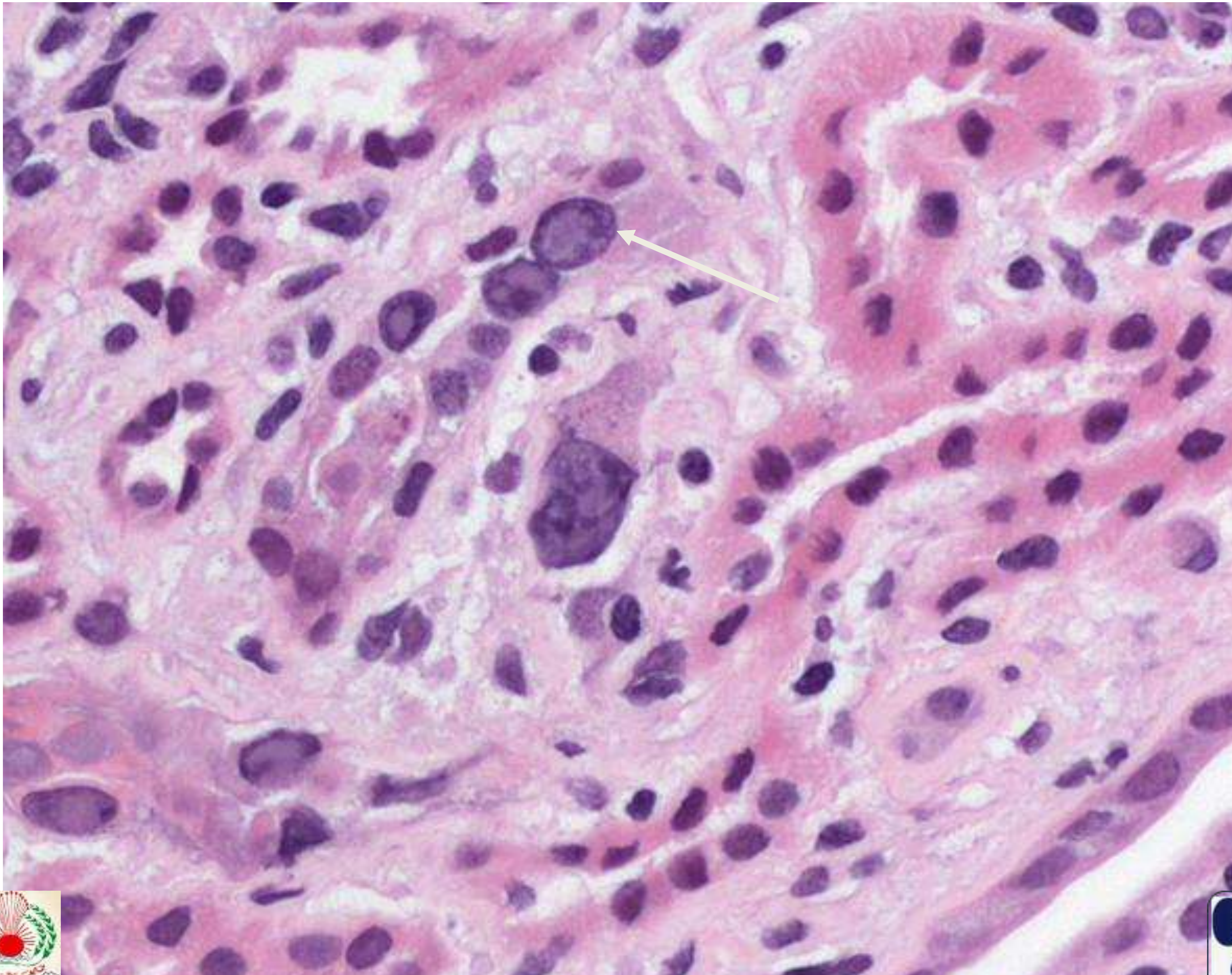
Polyoma V. (BK)

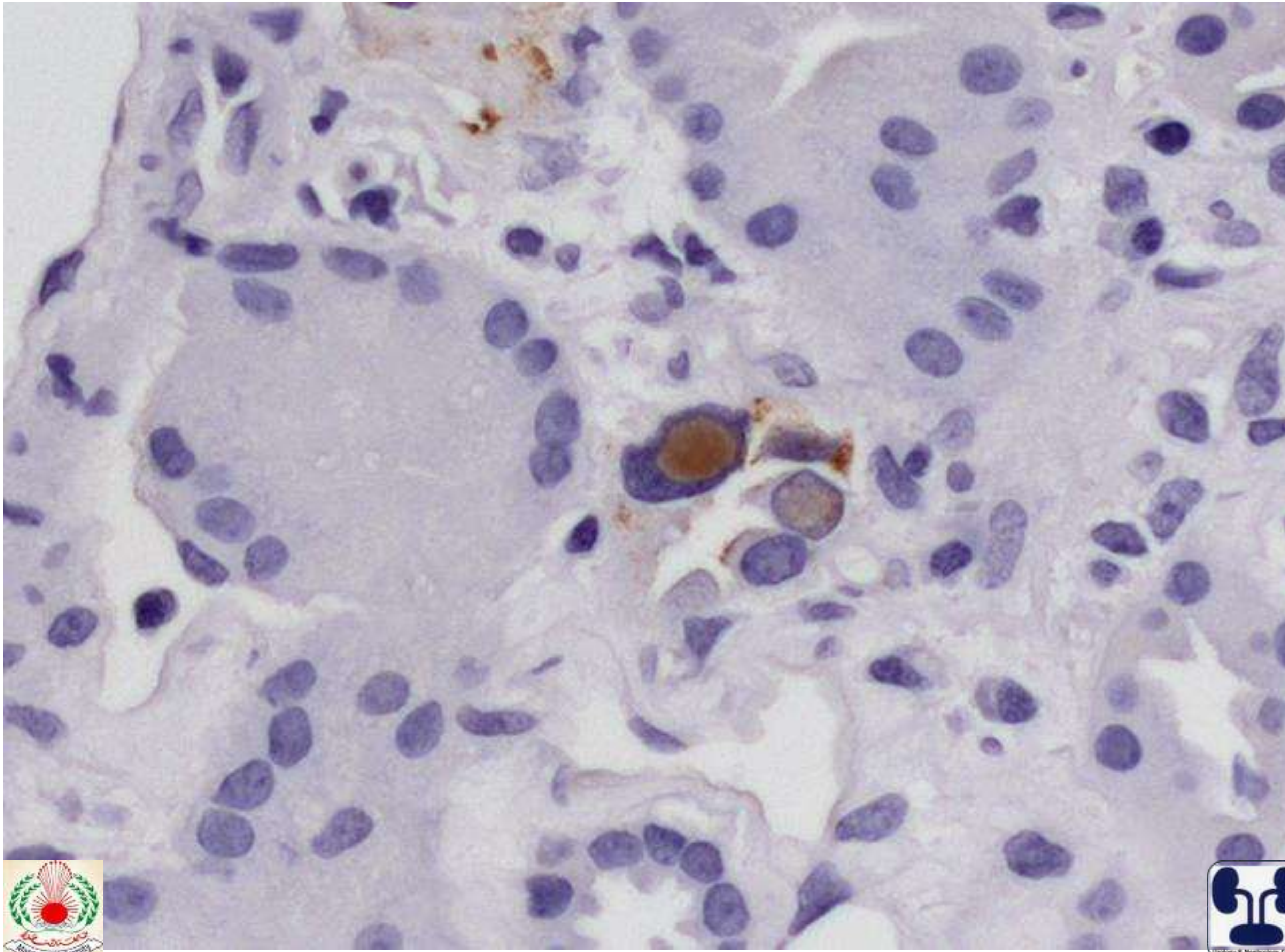
Clin Transplant 2012: 26 (Suppl. 24): 9–12 DOI: 10.1111/j.1399-0012.2012.01648.x

Clinical Transplantation

Topics Review in 2012

Polyomavirus nephropathy – recent pathological diagnostic problems and the report from the 2011 Banff meeting





Diagnosis

- Close follow up post-transplantation
- Biopsy
- Infection screen and prophylaxis
- Drug leveling
- Radiological assessment (renal scan)

Diagnosis

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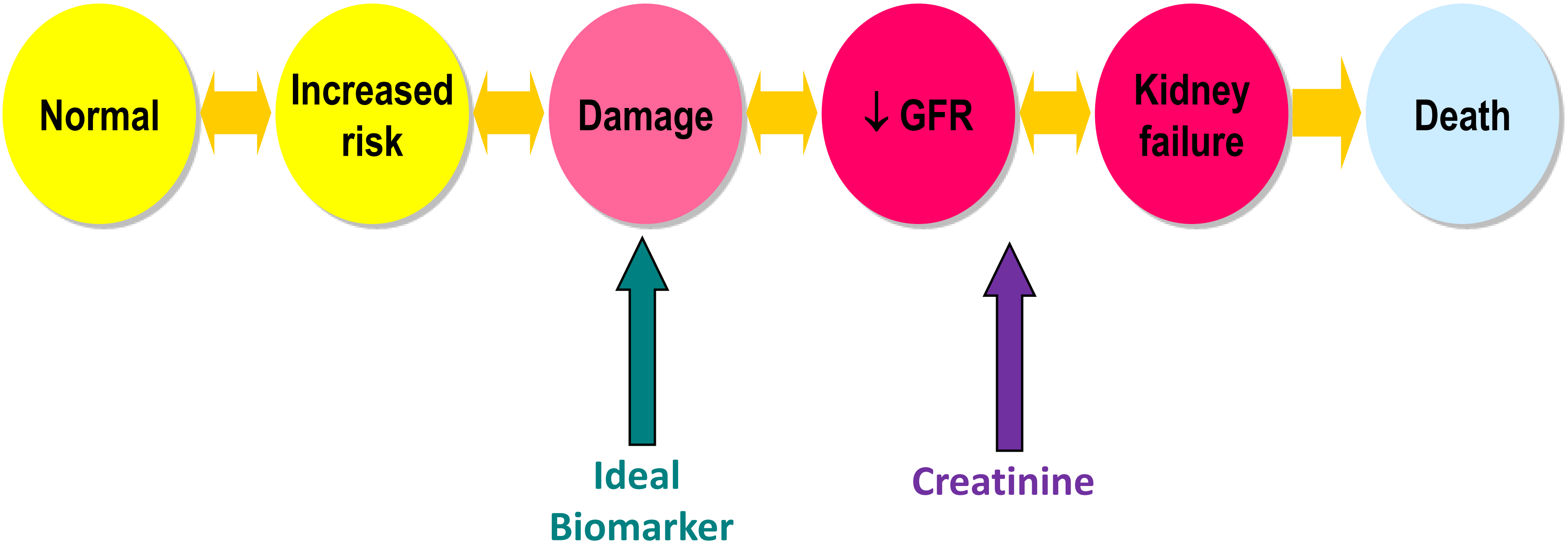
Which Biomarker Will Be Ideal?



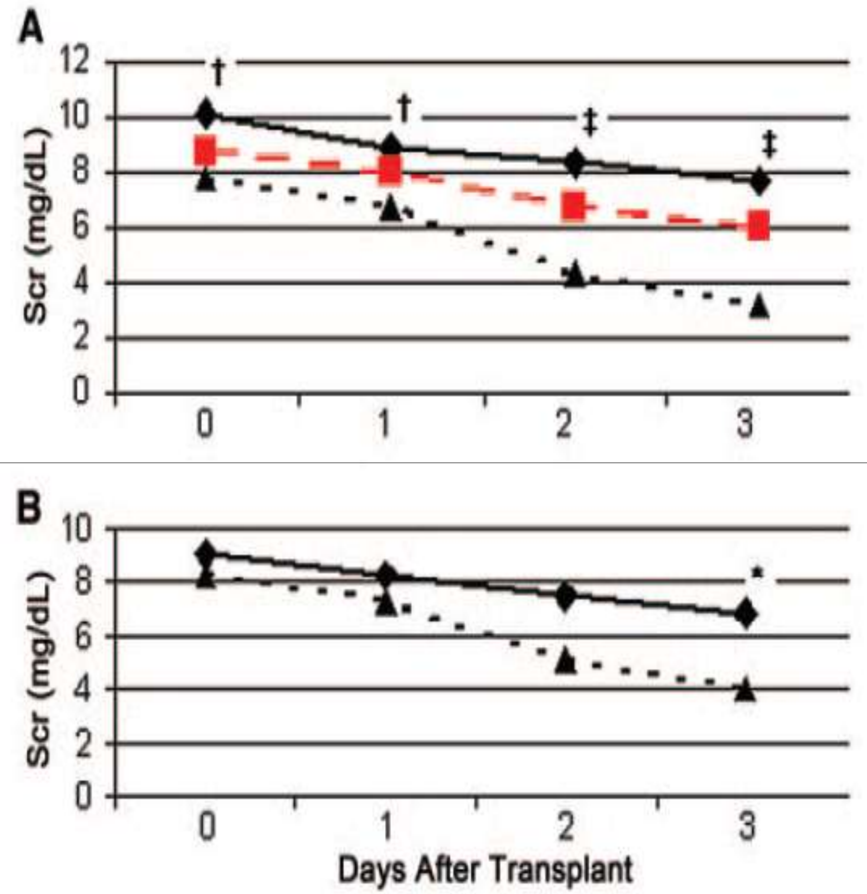
Candidate Biomarkers in AKI

- N-acetyl-β-D-glucosaminidase (NAG)
- Neutrophil gelatinase-associated lipocalin (NGAL)
- Kidney injury molecule-1 (KIM-1)
- Interleukin-18 (IL-18)
- Fatty acid binding protein (FABP)
- Cystatin C
- α-1-microglobulin
- β-2-microglobulin
- Matrix metaloprotinase-9 (MMP-9)
- Na+/H+ exchange isoform 3 (NHE3)
- Adenosine deaminase binding protein
- Alanine aminopeptidase
- Leucine aminopeptidase
- β-galactosidase
- α-glutathione S-transferase (α-GST)
- π-glutathione S-transferase (π-GST)
- Alkaline phosphatase
- Lactate dehydrogenase (LDH)
- Neutral endopeptidase
- Retinol binding protein

Candidate Biomarkers in AKI

Marker	Setting	N	Sen/Sp; ROC	
Cystatin C	ICU	85	0.82/0.95	Serum
	ICU	202	NR	
	ICU	29	0.5/0.5	
NGAL	Cardiac Surg Children	71	0.70/0.94	
NGAL	Cardiac Surg Children	71	1.0/.98	
	Cardiac Surg	81	0.73/0.78	
	Pediatric ICU	140	0.77/0.72	
	DGF	63	0.9/0.83	
IL-18	ICU	138	0.73	
	DGF	63	0.9	Urine
	Cardiac Surg	71	0.75	
	Pediatric ICU	137	0.54	
KIM-1	Cardiac Surg	40	0.83	
NAG	Cardiac Surg	40	0.69	
	ICU	26	0.845	

NGAL and IL18



J Am Soc Nephrol 21: 189–197, 2010.

Management

- Early detection
- Keep hemodynamics' stability
- Proper use of immunosuppression
- Antivirals
- Antirejection
- IRI (mainly cadaveric)
- Donor selection and organ preservation

Importance of IRI

Kidney international; December 2014.

IRI

Molecular Therapy, September 2010.

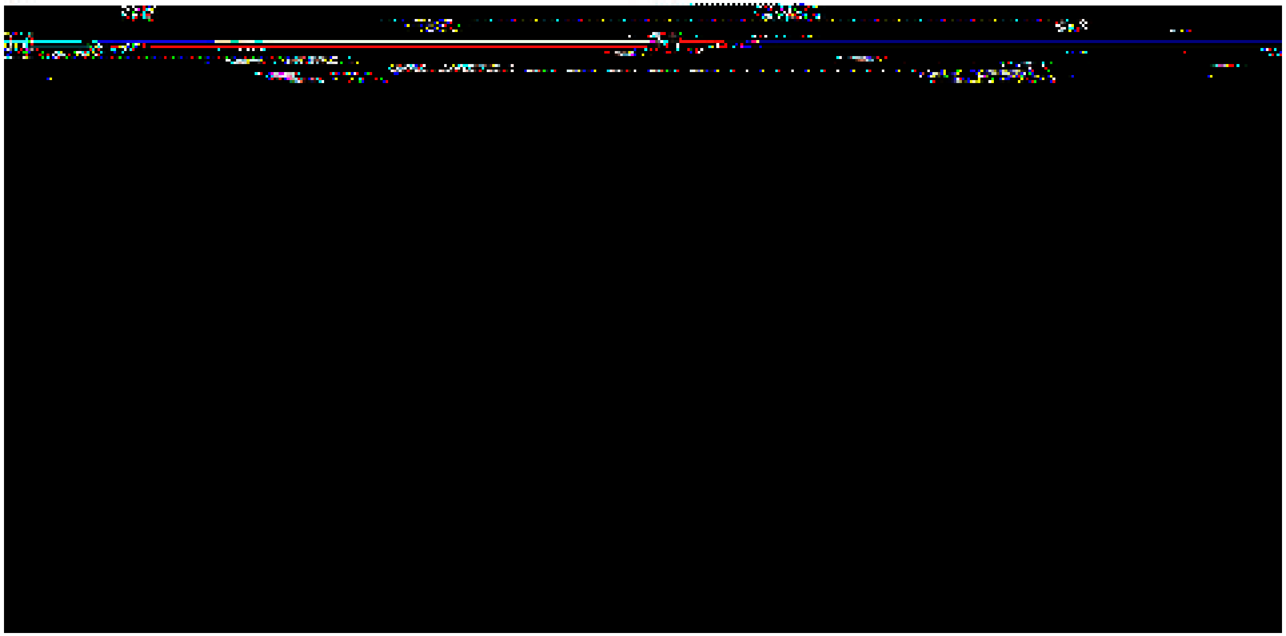
IRI

Molecular Therapy, September 2010.

Macrophage in IRI

J Am Soc Nephrol in press.

Macrophage in IRI



J Am Soc Nephrol 2011.

Macrophage in IRI

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J Am Soc Nephrol 2011

DCs in IRI

Published in final edited form as:
Kidney Int. 2012 May ; 81(10): 1015–1025. doi:10.1038/ki.2011.458.

The loss of renal dendritic cells and activation of host adaptive immunity are long-term effects of ischemia/reperfusion injury following syngenic kidney transplantation

Kikumi S. Ozaki, MD[1], Shoko Kimura, MD[1], Michael A. Nalesnik, MD[2], Rita M. Sico, BS[1], Matthew Zhang[1], Shinya Ueki, MD[1], Mark Ross, BS[3], Donna B. Stolz, PhD[3], and Noriko Murase, MD[1]

HO-1 In AKI

BASIC RESEARCH www.jasn.org

Heme Oxygenase-1 Regulates Myeloid Cell Trafficking in AKI

Travis D. Hull,*† Ahmed I. Kamal,* Ravindra Boddu,* Subhashini Bolisetty,* Lingling Guo,*† Cornelia C. Tisher,* Sunil Rangarajan,* Bo Chen,*† Lisa M. Curtis,*‡ James F. George,*† and Anupam Agarwal†‡

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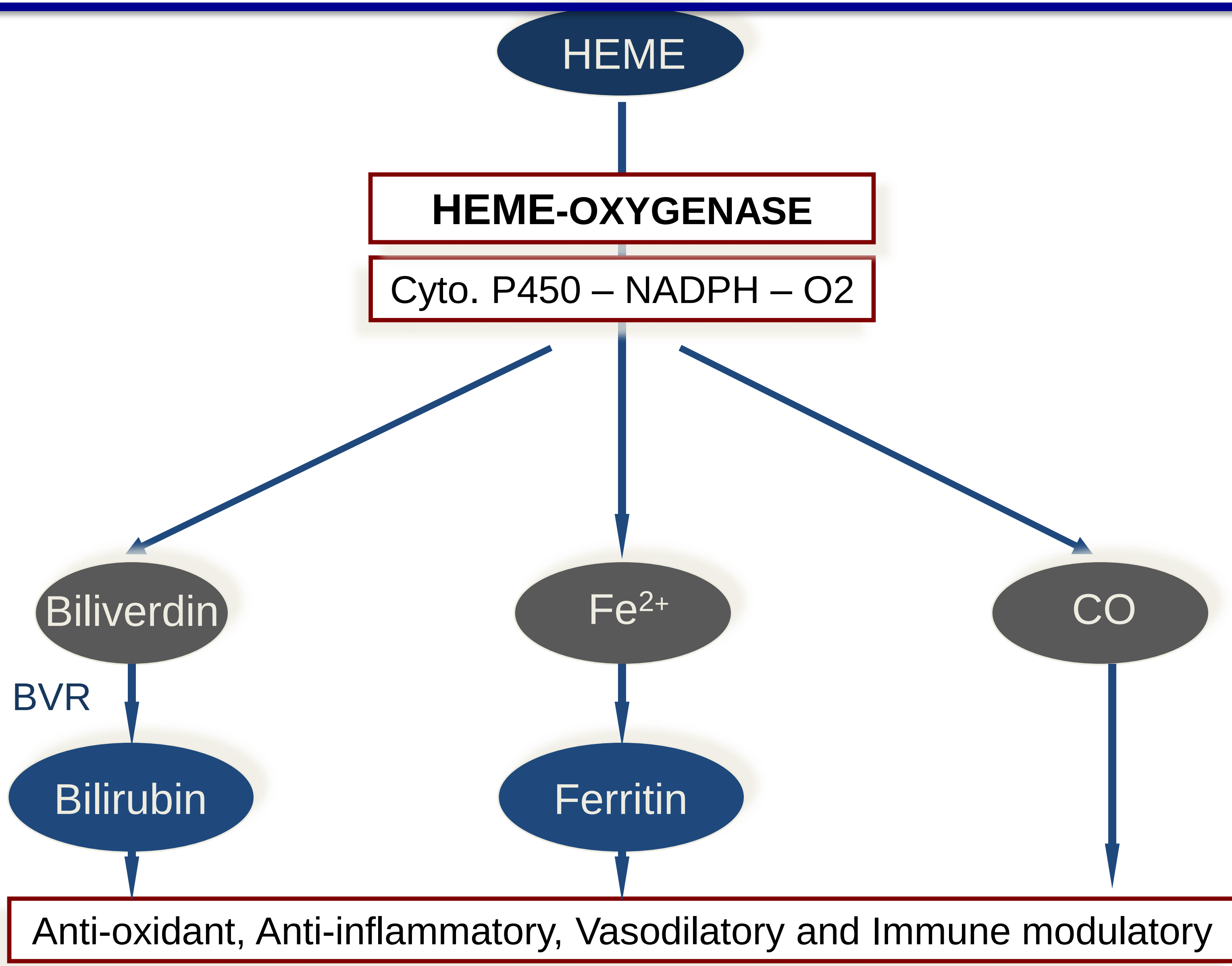
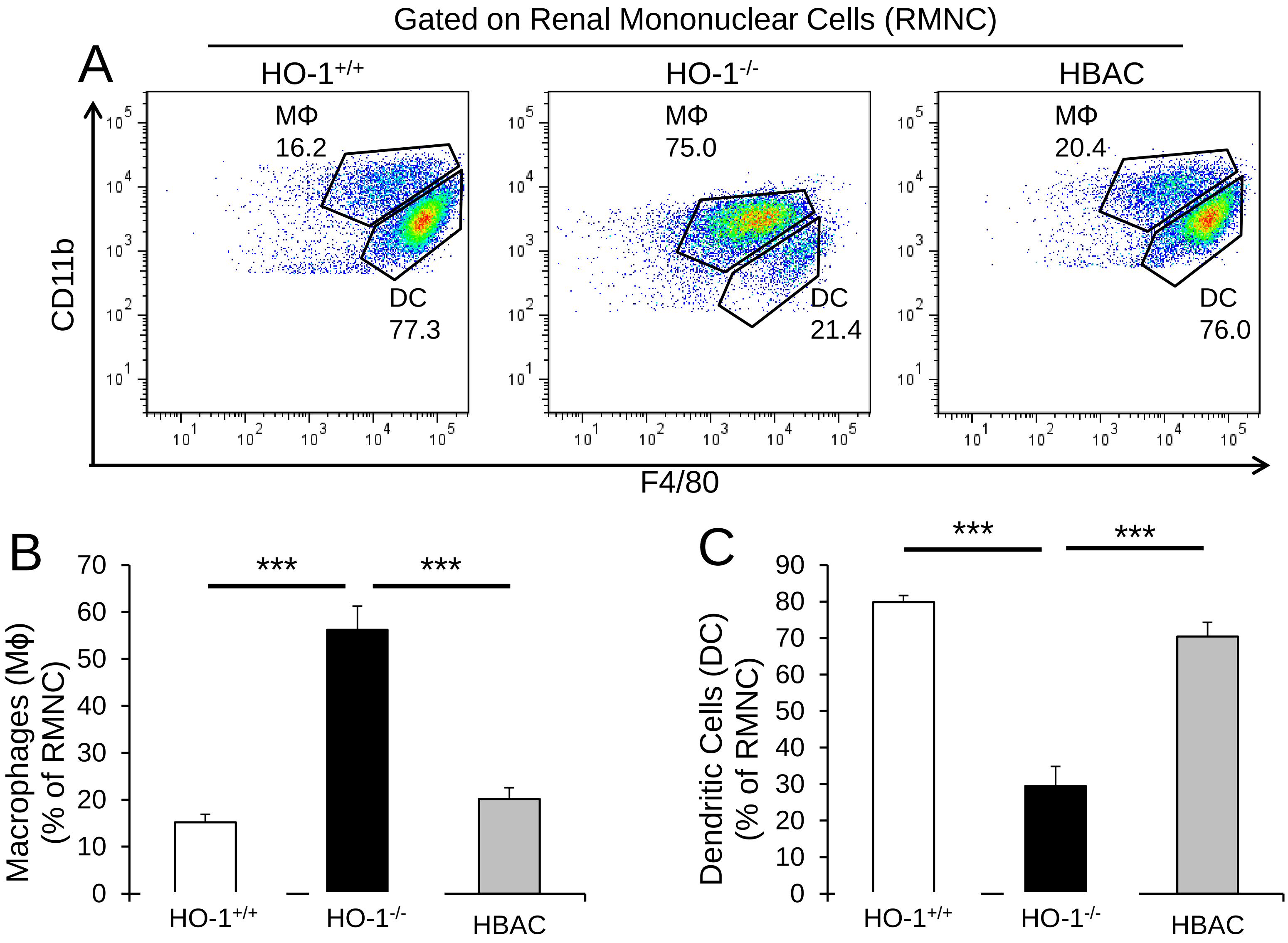
J Am Soc Nephrol in press.

Metabolic Pathway of Heme Oxygenase-1



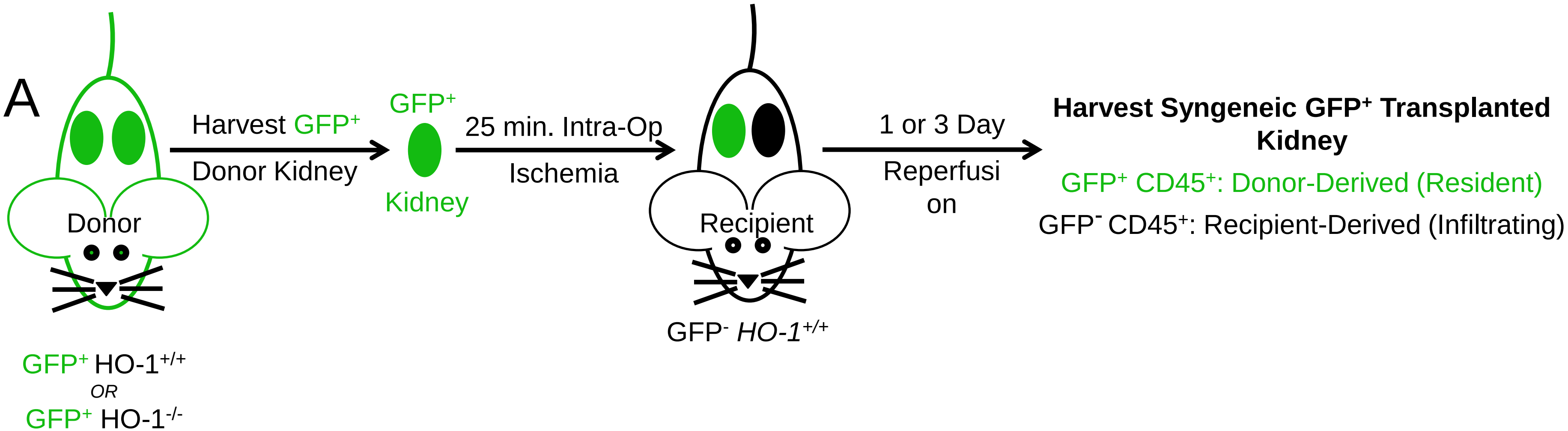
HO-1$^{-/-}$ Intra-Renal Resident DC Specifically Decrease after IRI



Is it a phenotypic shift?

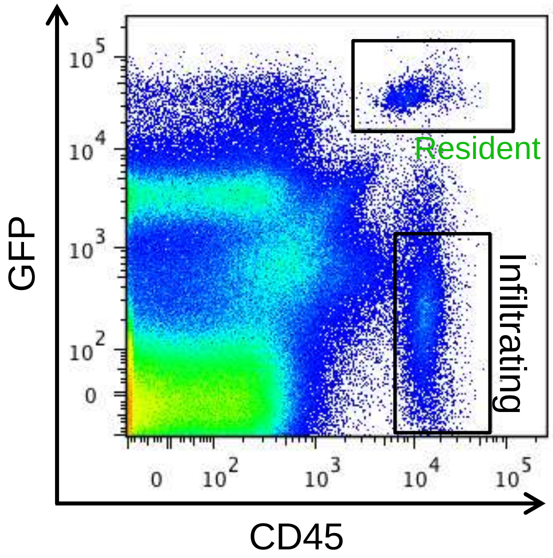
Possible explanations of findings in HO-1$^{-/-}$ mice:

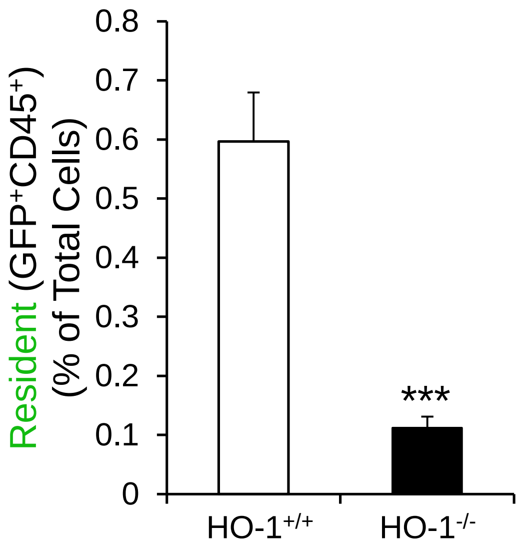
- Systemic pro-inflammatory milieu in HO-1$^{-/-}$ mice
- Phenotypic Shift (Renal DC acquire phenotypic characteristics of macrophages)
- Migration of renal DC from the kidney after IRI



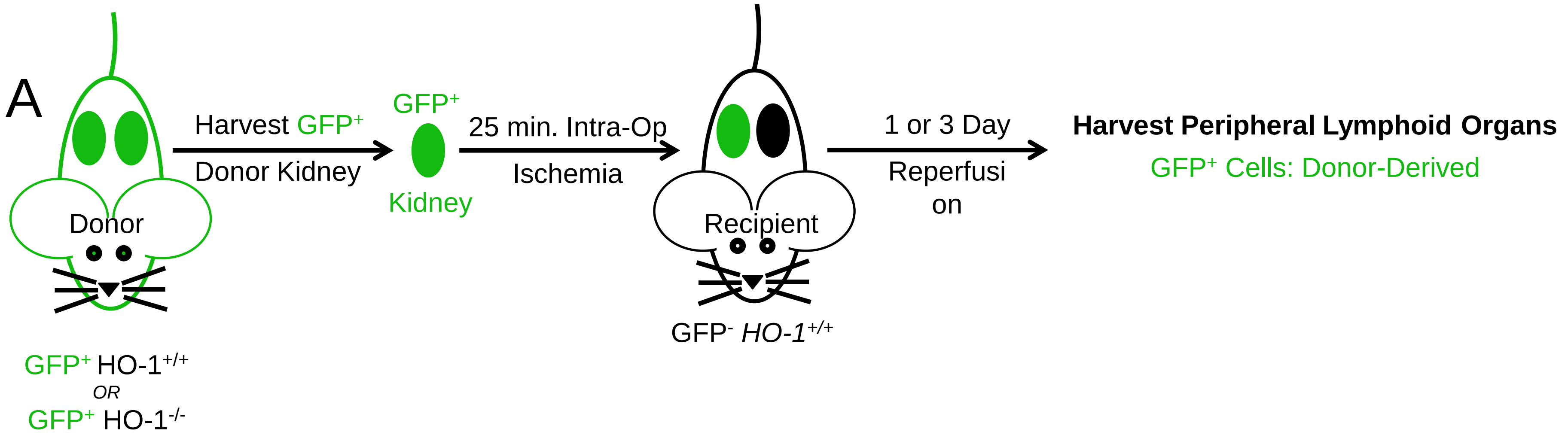
J Am Soc Nephrol in press.

HO-1 Deficiency Increases Trafficking of Resident RMNCs from the Kidney after IRI



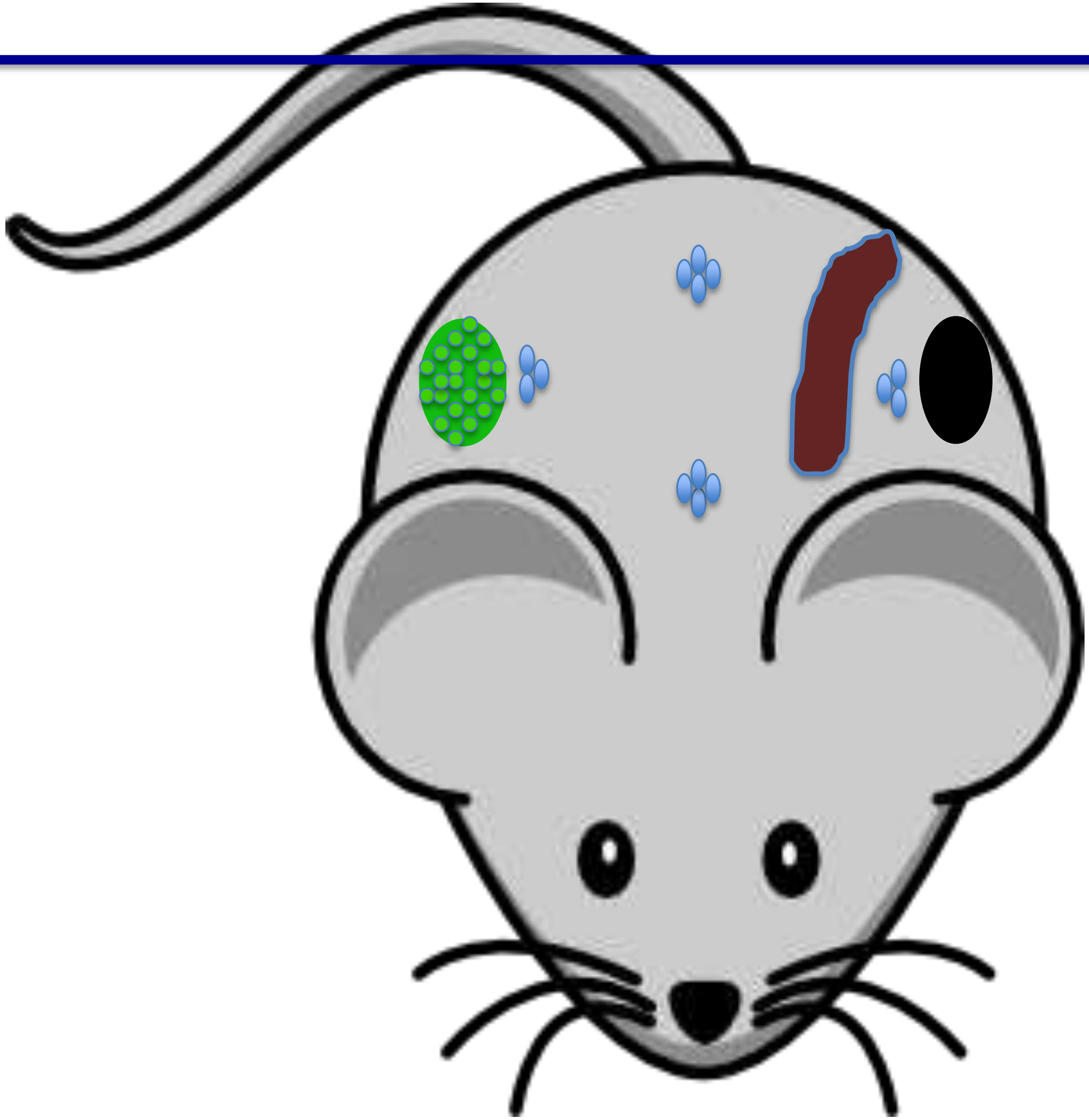


Where do these cells go?

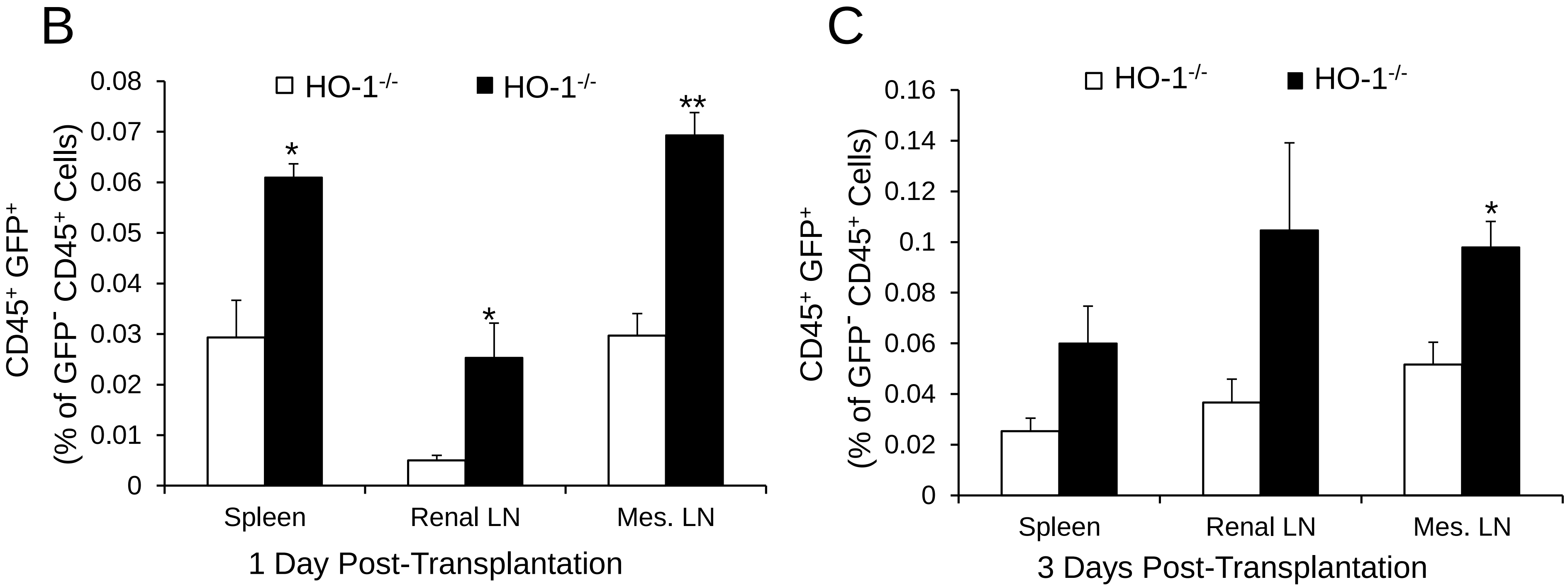


J Am Soc Nephrol in press.

Trafficking to the Peripheral Lymphoid Organs



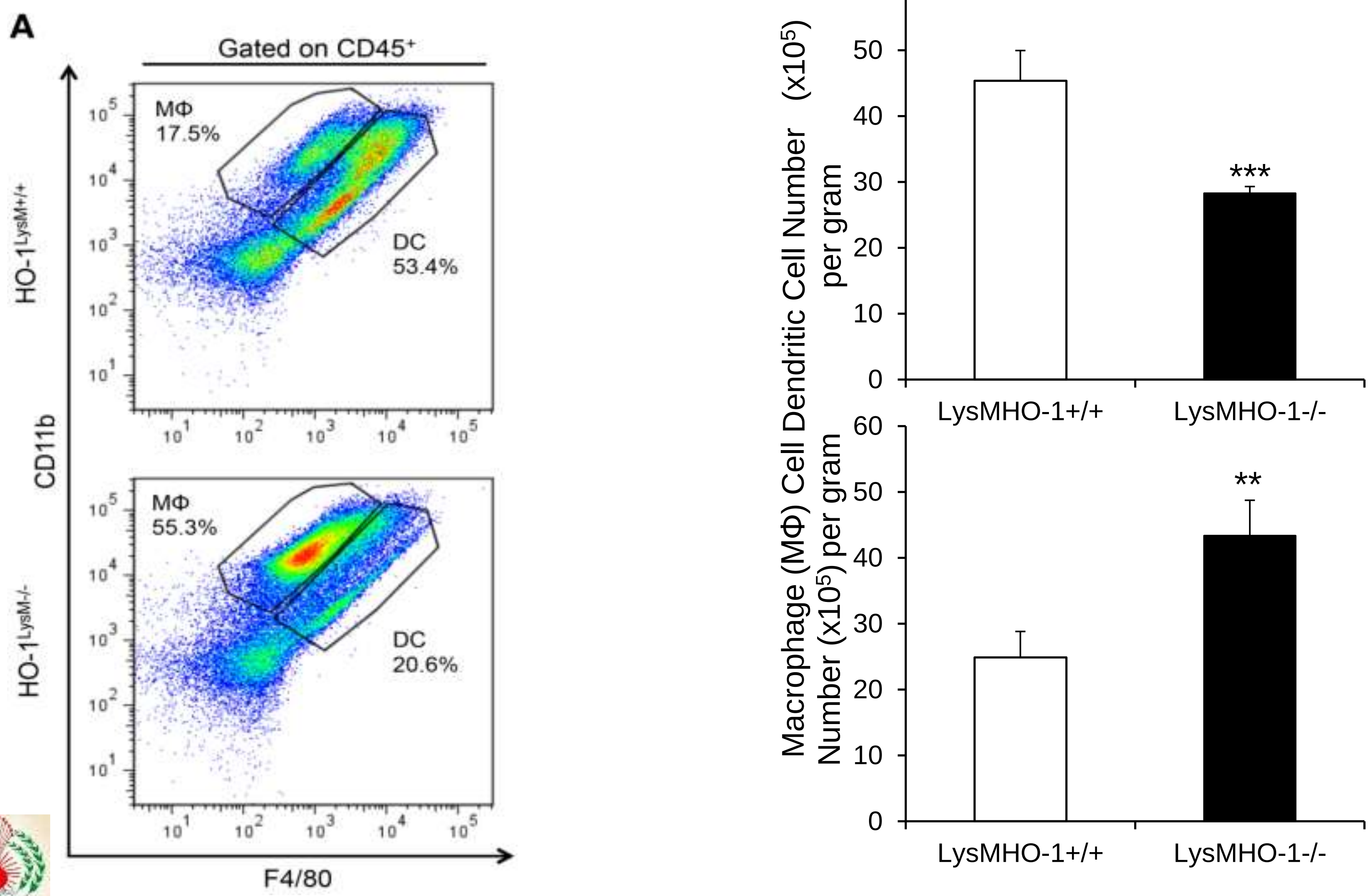
HO-1 Deficiency Increases RMNC Trafficking to the Peripheral Lymphoid Organs



J Am Soc Nephrol in press.

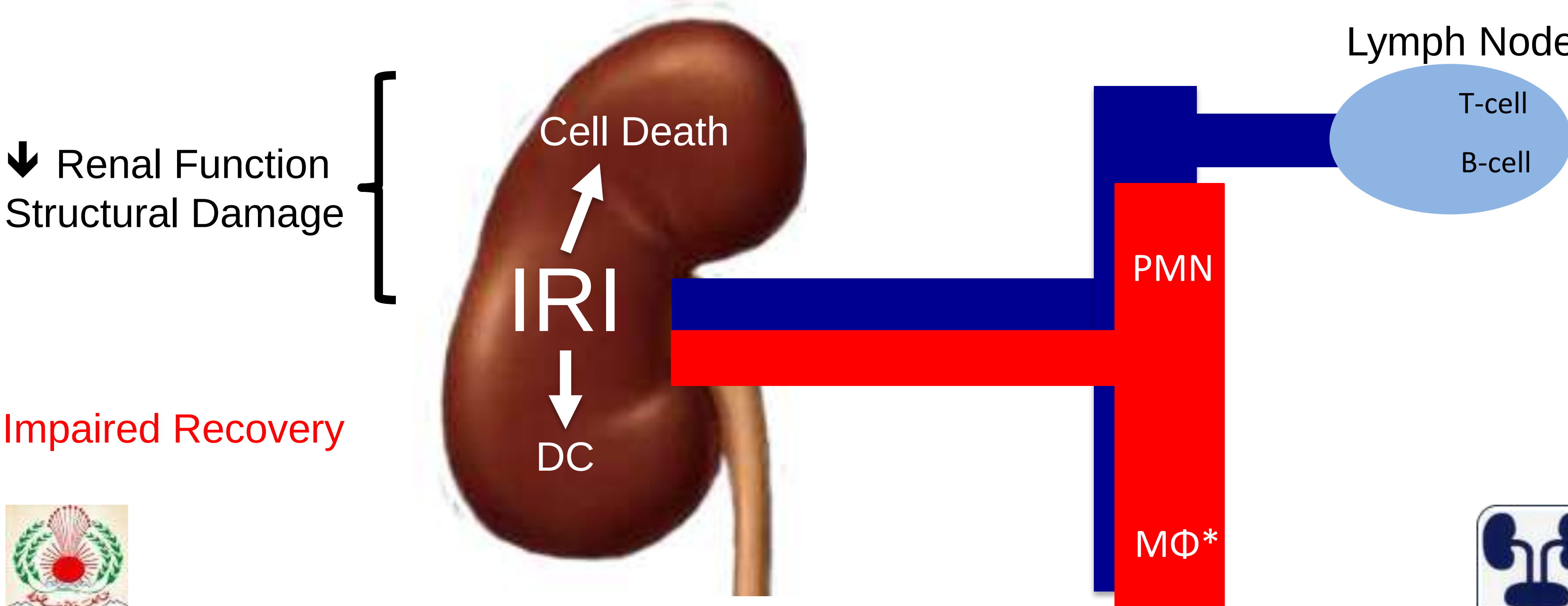
Myeloid HO-1 Regulates Trafficking of DC after IRI

3 days after 25 minutes of bilateral IRI



Conclusions

- HO-1 Expression plays an important protective role in IRI at the level of the
  - Renal Parenchyma (HO-$1^{-/-}$)
  - Intra-renal resident DC population (HO-$1^{LysM-/-}$)
  - Infiltrating macrophages (HO-$1^{LysM-/-}$) and PMN (HO-$1^{-/-}$)



Thank you

CMV in Organ Transplantation

1. Risk factors
2. Diagnosis
   - significance of viremia
   - role of invasive diagnostic procedures
3. Treatment options
   - oral vs IV
   - immunosuppression reduction
4. Prevention strategies

CMV in transplantation

- Single most important viral pathogen
  - "direct" effects (syndrome, tissue-invasive disease)
  - "indirect" effects (allograft rejection, other infections, PTLD)
- Risk factors for CMV disease:
  - serostatus (D+R- > D+R+/D-R+ > D-R-)
  - antilymphocyte antibodies
  - viral load
- Diagnosis
  - caveat: ubiquitous virus, especially in immunocompromised patients
  - presumptive: evidence of infection + compatible symptoms
  - definitive: demonstration of CMV in tissues

CMV in transplantation

- Prevention strategies
  - Prophylaxis
    - dominant strategy at US transplant centers
    - all pts at risk (R+, D+R-) receive antiviral agent post-transplant
  - Preemptive therapy
    - virologic monitoring guided antiviral therapy
- Late-onset CMV disease
  - after discontinuation of prophylaxis (~3 months)
  - ~15-30% of D+R- patients
  - associated with worse patient/graft survival
  - benefit of longer durations of antiviral prophylaxis [Humar AJT 2010]

CMV in transplantation

Treatment

- IV ganciclovir is "gold standard"
- po valganciclovir
  - non-inferior to IV ganciclovir in carefully selected patients [Asberg AJT 2007]
- Foscarnet & cidofovir rarely used due to significant toxicities (except resistant cases)
- Relapse in ~10-20%
  - Individualization of therapy
    - treat until viremia has cleared, minimum of 2 wks
- Reduction in immunosuppression generally recommended

CMV in transplantation

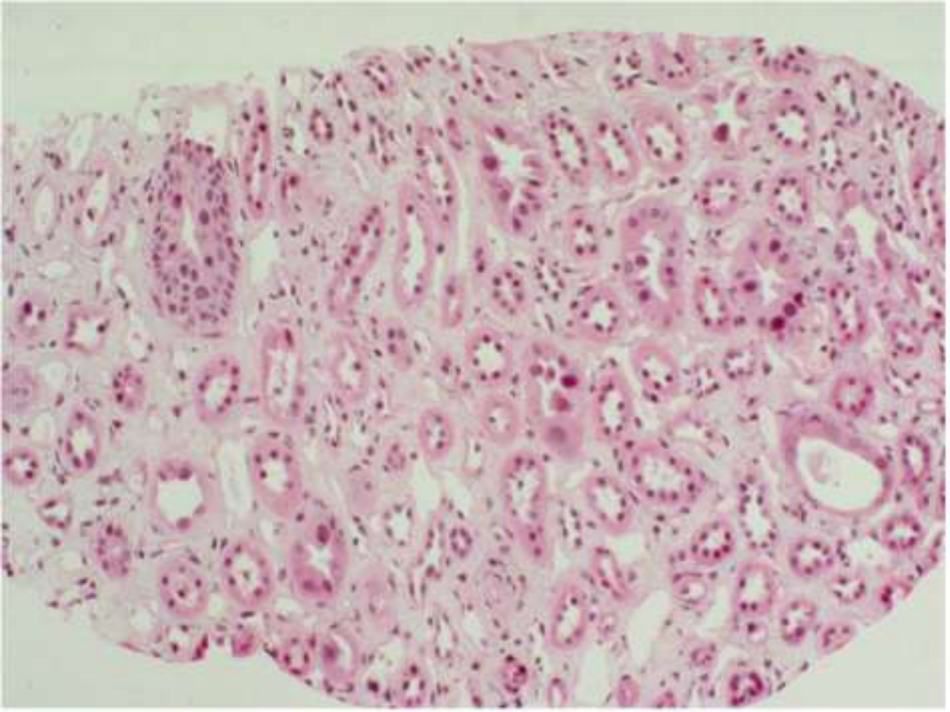
GI disease

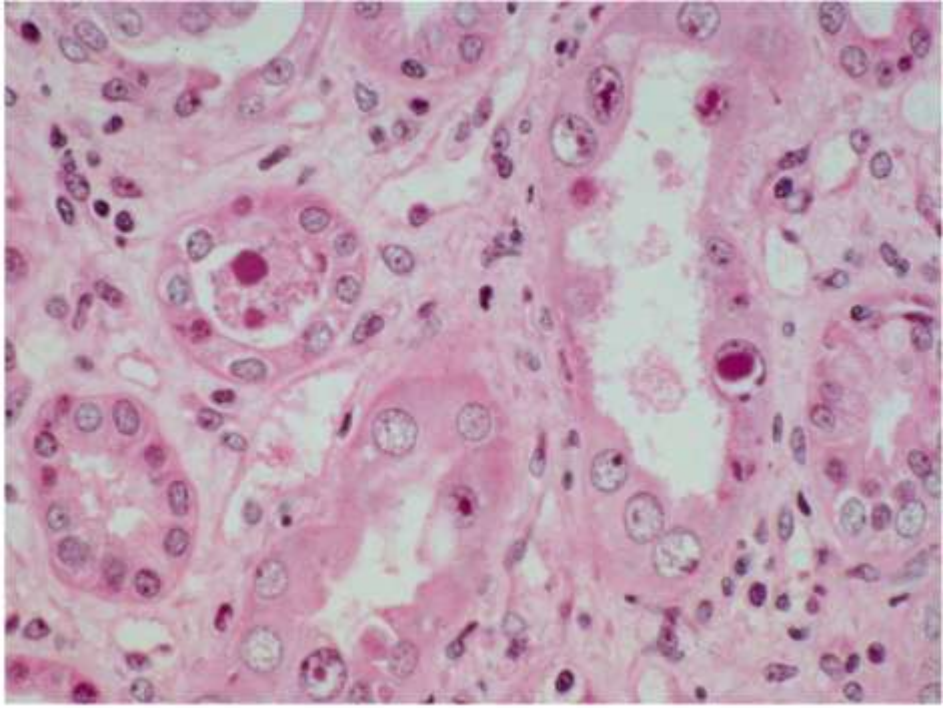
- most common form of tissue-invasive CMV (upper GI ~ lower GI involvement)
- no concomitant viremia in 10-20% (importance of endoscopy/biopsy)
- extent of disease on biopsy predictive of relapse
- may require longer durations of treatment than other forms of CMV disease

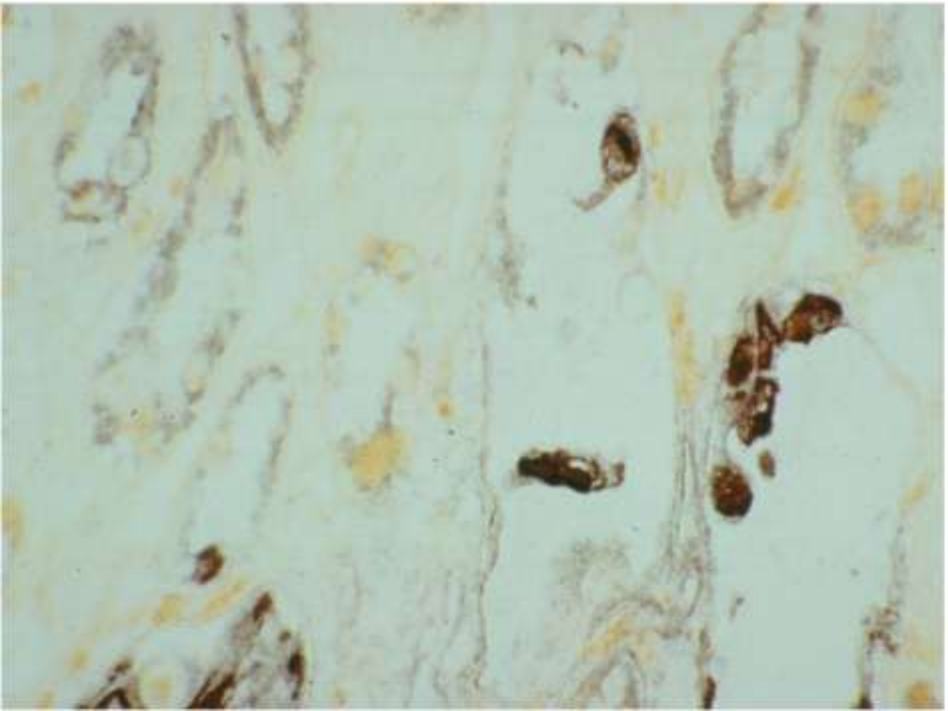
Unexpected renal allograft dysfunction late post transplant

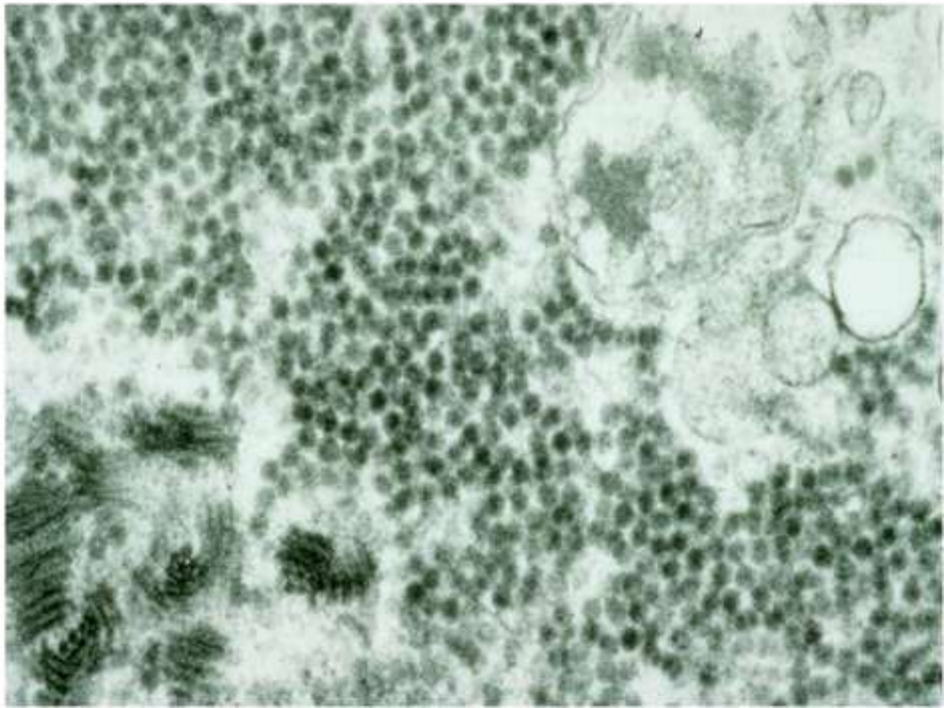
54yo man, routine f/u at 5 months post-transplant

- biopsy-confirmed rejection 1 month after transplant, treated with pulse dose prednisone (baseline Cr 1.2)
- Routine labs: Cr 1.6 (rest normal)
- Feels well, afebrile, physical exam is normal
- Meds: tac, pred, MMF, trim/sulfa







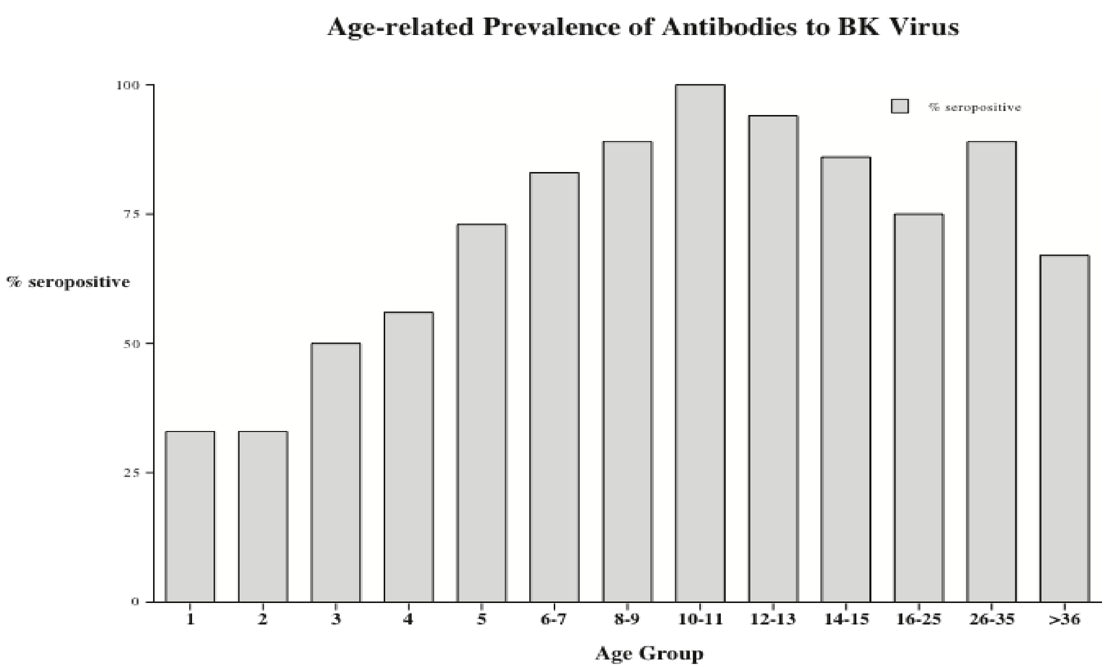


The most appropriate next step in the management of this patient would be:

1. Begin high-dose IV ganciclovir
2. Begin leflunomide
3. Begin low dose IV cidofovir
4. Reduce immunosuppression
5. Begin high dose ciprofloxacin

BK Virus Characteristics

- Polyoma virus (BK, JC, WU-1, KI, SV40)
- Non-enveloped, ds DNA, multiple genotypes (I thru IV)
- Small genome (~5000 bp)
- Acquired by respiratory (?other) route at young age (~80-100% of adults are seropositive)



BKVN Overview

Incidence & Risk Factors

- New (not newly recognized) complication of transplantation since ~1995
- Reactivation (urine ~30%, blood ~15%, biopsy ~1-5%)
- KP > K transplant
- Rejection and use of "newer immunosuppressive agents" are most commonly described risk factors
- significant cause of allograft dysfunction & loss [Lipshultz AJT 2005]

Clinical Features

- NO clinical symptoms (fever, etc.)
- Common presentations
  - Asymptomatic renal dysfunction
  - Non-response to treatment for rejection

BKV nephropathy: *Diagnosis*

Invasive (definitive)

- biopsy (can be focal → sampling error) [Drachenberg AJT 2004]
  - inclusions
  - immunohistoochemistry with SV40-specific antibodies (JC & BK will both be positive)
  - *in situ* hybridization
  - PCR

- Confirm diagnosis, staging/prognosis, identify concomitant process(es)

- Limitations: invasive (complications), cost, insensitivity (sampling error)

cont. BKV nephropathy: *Diagnosis*

<u>Non-invasive</u> (presumptive)

- urine cytology ("decoy cells")
- PCR (urine, blood)--DNA or mRNA
- EM (urinary "haufen")

- Limitations: occasional false negatives (sequence variation, assay variability, non-standardized)

- Advantages: non-invasive, relatively inexpensive, increased sensitivity over histopathology (sampling error), monitoring for preemptive therapy & disease course

BKVN Overview

Pathogenesis

- immunosuppression-->reactivation of latent infection
- occasional progression of reactivated infection to clinically significant disease

Prevention

- monitoring (blood or urine) and preemptive reduction in immunosuppression [Brennan et al Am J Transplant 2005]

Treatment (biopsy-confirmed disease)

- cautious reduction in immunosuppression
- uncertain role of antivirals (leflunomide, cidofovir, fluoroquinolones) or IVIG